

BRIEF COMMUNICATION

Lack of effectiveness of CO₂ cryotherapy for treatment of CIN

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conducted review (http://www.path.org/files/RH_cryo_white_paper.pdf), only two studies used CO₂ exclusively, and the only study in a low-resource setting [2] found residual disease in 97% of CIN3 patients.

Abdul-Karim [3] studied cervical conization specimens and concluded that a depth of necrosis

Cryotherapy is based on the property of gases to absorb heat when expanded suddenly. At the beginning, carbon dioxide (CO₂) was used as refrigerant, but soon nitrous oxide (N₂O) became the gas of choice due to lower temperatures achieved. Most of the publications on cryotherapy for CIN are based on experience with N₂O.

CO₂ cryotherapy is recommended, and currently used, in low-resource settings because it is inexpensive and widely available [1]. In a recently-

Table 1 Depth of necrosis produced by CO₂ cryotherapy

First freeze: 3 min Rest: 5 min Second freeze: 3 min		First freeze: 5 min Rest: 5 min Second freeze: 5 min	
Case	Deep (mm)	Case	Deep (mm)
1	3.8	8	3.5
2	2.5	9	3.1
3	2.8	10	2.9
4	2.8	11	2.2
5	2.1	12	2.6
6	2.4	13	3.9
7	2.8	14	2.9
		15	2.9
		16	3.1
		17	3.1

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of 4.8 mm is required to achieve ablation in 99.7% of CIN3 cases. This prospective study compared the depth of tissue destruction achieved by two CO₂ cryosurgical schemes. Women aged 30–55, scheduled for hysterectomy for nonmalignant disease were eligible for this study. At the beginning, we planned to include 60 patients, but the poor outcomes led us to publish data based on 17 patients.

Cryotherapy was performed using the LL100 Cryosurgical System with a T-1905 Exocervical cryo-tip (Wallach, Connecticut, USA). We used two therapeutic schemes: the freeze–thaw–freeze cycle was 3–5–3 min in the first group and 5–5–5 min in the second one. Following the manufacturer recommendations to avoid ice blockage of the equipment, it was purged every 20 s by pushing the defrost button for less than 1 s, then the freezing button was pushed again to continue treatment. Hysterectomy was performed 22- to 25-h postcryotherapy.

The unfixed cervix was separated from the uterus; the anterior and posterior lips were separated by cutting through 3 and 9 o'clock positions, parallel to the axis of the canal, and fixed in formalin for at least 20 h. Then several sections (2–3 mm thick) were cut perpendicularly to the mucosal surface in a plane parallel to the axis of the canal. 12 to 20 slides were obtained for each case and reviewed to determine the depth of necrosis, measured from the epithelial surface by superimposing a micrometer in the 10× eyepiece of the microscope.

We obtained data from 17 women (Table 1 and Fig. 1). The mean necrotic depth was 2.74 mm for the 3–5–3 min protocol and 2.97 mm for the 5–5–5 min protocol ($P=0.38$, two-sided t -test; $P=0.20$, nonparametric Wilcoxon test). This suggested that increasing the application time did not meaningfully improve the effectiveness of the treatment. The average depth of necrosis overall was 2.88 mm (95%CI=2.62–3.13). A one-sided hypothesis test of whether the mean depth of necrosis was less than 4.8 mm yielded a p -value of 1.5×10^{-11} (t -test) and 1.6×10^{-4} (Wilcoxon test), indicating that it is highly unlikely that a depth of 4.8 mm could be achieved. Our study suggests that CO₂ cryotherapy might not be able to achieve sufficient depth of tissue necrosis. This might explain the high rates of failure observed in a pilot clinical study conducted

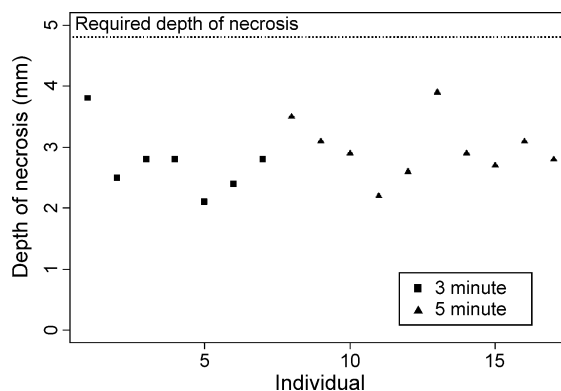


Figure 1 Depth of necrosis in the cervixes of women treated with CO₂ cryotherapy. Observed depth of necrosis in millimeters under the two protocols. The 3–5–3 min protocol is shown as squares and the 5–5–5 min protocol is shown as triangles. The depth of necrosis required to eliminate CIN3 lesions is marked by the dotted line. None of the women achieved the required depth of necrosis using the CO₂ cryofreezing.

in Peru (unpublished data) and could be a source of concern for other similar programs.

Ice blockage of the CO₂ cryotherapy equipment was a frequent problem in developing countries that has been solved “purging” the cryo-gun by pushing the defrost button every 20 s during the freezing process. However, based on our results and those of Boonstra et al. [4] showing that freezing longer than 5 min did not appreciably increase the cryonecrosis, we now have serious doubts about the capacity of CO₂ cryotherapy to cure CIN3. The consistency of our findings prompted us to report early findings, but additional prospective studies on the subject are urgently needed.

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